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# Fairness via formulations: A review of cosmetic skin-lightening ingredients

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**Synopsis**

Skin-lightening cosmetics are in big demand across Asia, and the quest for fairness has led to identification of many new ingredients. The mechanisms underlying pigmentation have been researched extensively and the knowledge is being updated regularly. This review serves to list the ingredients that are commercially available for that purpose and the modes of action through which the lightening is effected. Skin-lightening ingredients are also classified based on their sources; it is significant that far more botanicals have made the list than have synthesized compounds. Tyrosinase inhibition as a means of skin lightening is still the most reported method, followed by other methods such as Mitf inhibition, down regulation of MC1R activity, interference with melanosomal transfer, and melanocyte loss.

## INTRODUCTION

The definition of fair skin is given as "not dark and free from spots, specks, dirt or imperfection; unblemished; clean; pure." The booming cosmetics industry in recent decades can be partly attributed to the elusive search for fair and flawless skin (1,2). With the vast information that is accessible in the 21st century, one has an option to choose methods ranging from that of Cleopatra (soaking in donkey milk that is rich in AHA) to recent advances in skin-lightening procedures such as dermabrasion, ultrasound, and laser therapies, to name a few (3–9).

Skin-lightening agents are any ingredient or combination of ingredients that interfere in any step of the melanogenesis pathway, melanin transfer, or desquamation that results in lowering pigmentation on the surface of the skin (10). Skin-lightening cosmetics are in big demand across the world, and this review serves to list the ingredients that are commercially available for that purpose and the modes of action through which the lightening is effected. There are many reports of skin-lightening agents obtained from both natural and synthetic sources. However, many ingredients in their original form may not be compatible in cosmetic formulations for application to the skin due to various factors such as cytotoxicity, insolubility, instability, and their sensitive nature to external conditions. However, consistent efforts are being made by industry to arrive at compatible, minimally toxic, and highly efficacious ingredients that serve the purpose.

## PIGMENTATION IN SKIN

The color of our skin is due to the polymeric, amorphous, non-proteinaceous pigment called melanin. Melanin is produced in the skin through a biochemical process called melanogenesis. Dermal melanin is produced by melanocytes, which are found in the stratum basale of the epidermis. The pathway of melanogenesis as elucidated by Raper (18) and Mason (19) is shown below (Figure 1).

The difference in skin color between fair people and dark people is due not to the number (quantity) of melanocytes in their skin, but to the melanocytes' level of activity (quantity and relative amounts of eumelanin and pheomelanin). In skin that exhibits a dark color the melanosomes are well distributed in the keratinocytes, which absorb radiation (11).

Pigmentation in skin is determined by various physiological processes occurring at different stages (12):

(a) Development of melanocytes

(b) Density of melanocytes

(c) Expression of the enzymatic and structural constituents of melanosomes

(d) Synthesis of melanin

(e) Transport of melanosomes to dendrites

(f) Transfer of melanosomes to keratinocytes

(g) Distribution of melanin in the supra basal layers of the skin

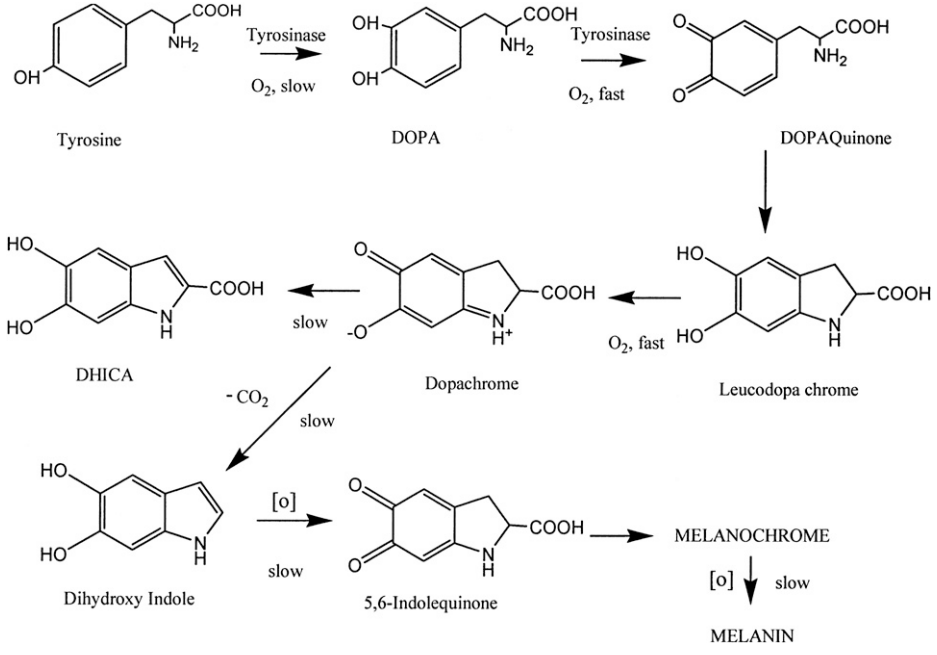


**Figure 1.** Raper-Mason pathway of melanogenesis.

The first three stages are completely controlled genetically, while the next four stages are targets for manipulation through skin-lightening agents. The most important factor other than inheritance affecting skin pigmentation is ultraviolet (UV) radiation (Figure 2). Exposure to UV triggers the following reactions that cause darkening of the skin (13–15):

(a) Oxidation and polymerization of melanin

(b) Redistribution of melanosomes

(c) Activation of MITF (microphthalmia-associated transcription factor) leading to increased melanin content

(d) Increase in expression of α-MSH (melanocyte-stimulating harmone) leading to enhanced melanocyte responses

(e) Transfer of melanin from the lower to the upper epidermis to prevent damage from radiation

A very effective method of reducing UV-induced pigmentation would be to incorporate sunscreens in the vehicle used for skin lightening. Physical sunscreens like zinc oxide and titanium oxide are available to suit delivery vehicles like creams, lotions, gels, etc. Chemical sunscreens may be chosen from a variety of synthetic compounds such as ethyl hexyl methoxy cinnamate, butyl methoxydibenzoylmethane, phenyl benzimidazole sulfonic acid, and other substituted salicylates.

## SKIN LIGHTENING

Skin-lightening agents are those that cause depigmenting activity on human skin, and they have been widely used in dermatology and cosmetics. A huge number of actives (both from biological sources and synthetic chemical compounds) have been reported in the literature (16,17). Their mechanism of action is generally through:

(a) Tyrosinase inhibition

(b) Mitf inhibition

(c) Down regulation of MC1R activity

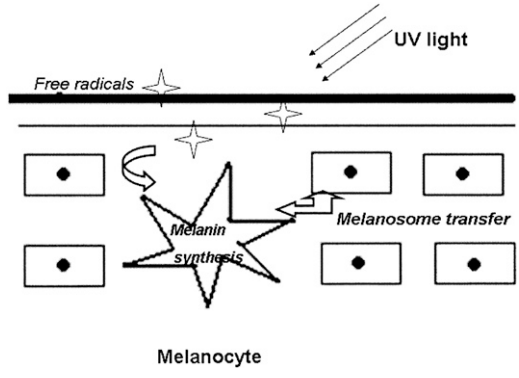


**Figure 2.** Schematic representation of the effect of UV rays on skin leading to pigmentation.

(d) Interference with melanosome maturation and transfer

(e) Melanocyte loss, exfoliation

Successful treatments mostly combine two or more modes of action to achieve a synergistic effect.

## CLASSIFICATION OF SKIN-LIGHTENING INGREDIENTS

Skin-lightening ingredients can also be classified by their source, such as the classes to which they belong. The important classes are:

(i) Chemical tyrosinase inhibitors (hydroquinone and similar type of compounds)

(ii) Botanicals (essentially from plants and algae)

(iii) Anti-oxidants

(iv) Vitamins—A, B, C, E

(v) Peptides

(vi) Alpha and beta hydroxyl acids and derivatives

## TYROSINASE INHIBITION

The inhibition of tyrosinase is the most widely reported screening method in the literature for skin-lightening ingredients. Tyrosinase is a copper-containing enzyme present in melanocytes that catalyzes the production of melanin. The biosynthetic pathway of melanin synthesis was first elucidated by Raper (18). Tyrosinase inhibition may be achieved by inhibitors from chemical or biological sources.

*(i) Chemical tyrosinase inhibitors (Figure 3).* There has been tremendous activity in the identification of tyrosinase inhibitors that are of synthetic origin. Such compounds are generally highly pure and potent. Synthetic compounds of various classes like hydroquinone and derivatives, phenolic amines, coumarins, chalcone analogs, hydroxy stilbene derivatives, benzaldehyde analogs, biphenyls, and trihydroxy flavones have been studied for their tyrosinase inhibitory properties (21–33).

However, many of these compounds have been screened through *in vitro* assays and their efficacy and adverse effects need to be established through clinical trials. Chemical compounds with depigmenting activity have been used in cosmetics for a long time. Some of the best known tyrosinase inhibitors are hydroquinone, kojic acid, and similar types of compounds.

(a) HYDROQUINONE AND DERIVATIVES. Hydroquinone is considered to be the gold standard for depigmenting agents. Hydroquinone interacts with copper at the active site of the enzyme tyrosinase, thus decreasing its activity by nearly 90% (34). It not only limits tyrosinase but also oxidizes membrane lipids and proteins through generation of reactive oxygen species (35). The radicals generated inhibit cellular metabolism by affecting DNA and RNA synthesis (36). It is generally administered at concentrations ranging from 1.5% to 5% concentration. The use of hydroquinone in cosmetics has diminished because of adverse side effects due to its cytotoxic nature. Monobenzyl ether of hydroquinone

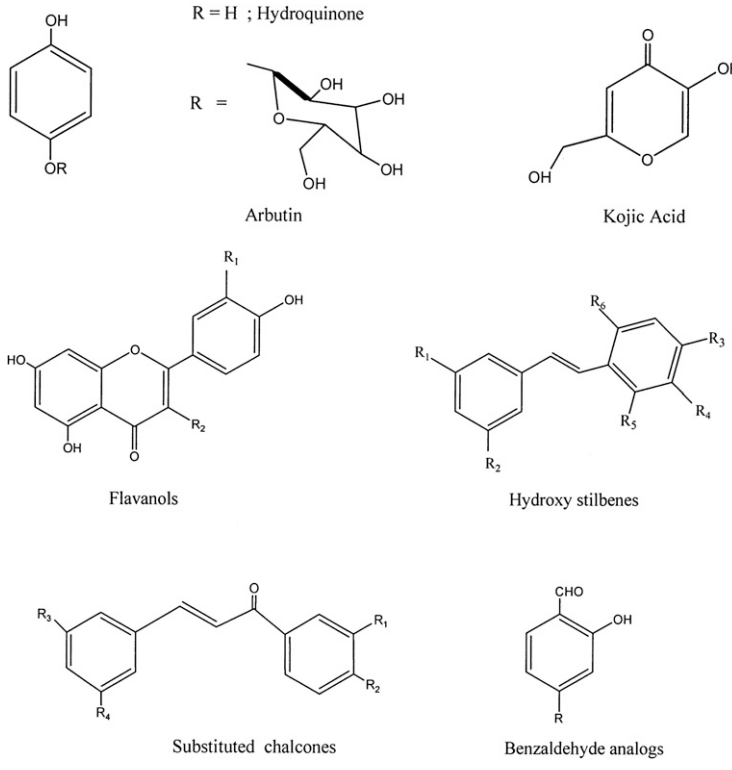


**Figure 3.** Structures of some skin-lightening agents.

(MBEH) and monomethyl ether of hydoquinone (MMEH) also demonstrate tyrosinase inhibitory properties (37–39). Further, they also cause melanocyte loss through generation of free radicals. However, the use of these compounds for depigmentation is limited by their adverse effects, similar to those of hydroquinone.

(b) ARBUTIN. Arbutin is a naturally occurring β,D-glycopyranoside derivative of hydroquinone. Although it shows tyrosinase inhibition, it is not found to affect RNA synthesis as does hydroquinone. The α-derivative shows a stronger inhibitory effect on tyrosinase and melanosome maturation (40,41). It is also present in many of the botanical extracts. Arbutin is highly pH-sensitive and can hydrolyze to hydroquinone at both acidic and alkaline pH. Hence, care should be taken during use in commercial skin-lightening products.

(c) KOJIC ACID. Kojic acid is a powerful tyrosinase inhibitor. It functions by the chelation of copper at the active site of the enzyme tyrosinase (42). Further, it acts as an antioxidant and a free radical scavenger. Although powerful, the use of kojic acid is under scrutiny by dermatologists because of its adverse side effects such as allergic dermatitis (43). It is found to be unstable in formulations and may also cause discoloration. Some stable derivatives, such as kojic acid dipalmitate, are being used to enhance effectiveness by enhanced skin penetration. Thus there exists a demand for safe and effective alternative botanicals as preferred skin-lightening ingredients.

*(ii) Botanical extracts.* Extracts mostly contain a combination of two or more classes of compounds that work synergistically to achieve skin lightening. Botanicals connote nature and are hence more acceptable to people. Further, a large number of yet undiscovered plants are available to provide for exotic products and claims for cosmetics. However, it should also be observed that natural extracts may be highly unstable and may not be compatible within formulations. A large number of ingredients (Table I) have been studied for tyrosinase inhibition and have been processed to make them viable for use in cosmetic products. These are available commercially through suppliers for use as skin-lightening agents.

*(iii) Antioxidants as skin-lightening agents.* Antioxidants serve to reduce oxidation of tyrosine to DOPA quinone and therefore are shown to have skin-lightening activity (64). In addition, they act in the melanogenesis pathway, reducing the synthesis of melanin. Exposure to UV radiation results in the generation of free radicals. It has been identified that ROS (reactive oxygen species) are able to oxidize tyrosinase and DOPA to melanin, and this is one of the major causes for tanning (65). Although antioxidants are present in tissues, they may not be able to reduce the radicals, depending on the extent of UV exposure. Inflammation is a source of free radicals. Hence the quenching of free radicals would also help in reducing the synthesis of melanin, thereby contributing to skin depigmentation effects (66). The use of phytic acid, glutathione (Figure 4), and ubiquinone as popular skin-lightening agents is due to their strong antioxidant nature (67–68). Melanin synthesis in melanocytes is accompanied by the generation of hydrogen peroxide that can lead to the formation of ROS that further increase the proliferation of melanocytes.

**Table I**
Botanicals That are Mostly Used in Skin-Lightening Cosmetics

| S. No. | Extract | Type | Reference |
|---|---|---|---|
| 1 | *Morus alba* extract | 2-Oxyresveratrol | 44 |
| 2 | *Aloe barbadensis* leaf extract | Aloesin | 45 |
| 3 | *Crocus sativus* extract | Kaempferol | 46 |
| 4 | *Uva ursi* | Arbutin | 47 |
| 5 | Licorice extract | Glabridin | 48 |
| 6 | *Camelia sinesis* extract | ECG | 49 |
| 7 | *Phylanthus embelica* extract | Vitamin C | 50 |
| 8 | *Citrus limonum* extract | Hisperidin | 51 |
| 9 | *Punica granatum* extract | Ellagitannins | 52 |
| 10 | *Vitis vinifera* (grape) fruit extract | Procyanidins | 53 |
| 11 | Anise extract | Anisic acid | 54 |
| 12 | Cumin seed extract | Cumic acid | 55 |
| 13 | *Cinnamonum cassia* extract | Trans-cinnamaldehyde | 56 |
| 14 | *Artocarpus lakoocha* heartwood extract | 2-Oxyresveratrol | 57 |
| 15 | *Purus comunis* (pear) extract | Arbutin | 58 |
| 16 | Geranium extract | Ellagic acid | 59 |
| 17 | *Ramulus mori* extract | 2-Oxyresveratrol | 60 |
| 18 | Ginseng extract | p-Coumaric acid | 61 |
| 19 | *Malpighia punicifolia* (*Acerola*) fruit extract | Polyphenols | 62 |
| 20 | *Mushroom* (*Agaricus blazei Muril*) extract | Tri-terpenoids | 63 |

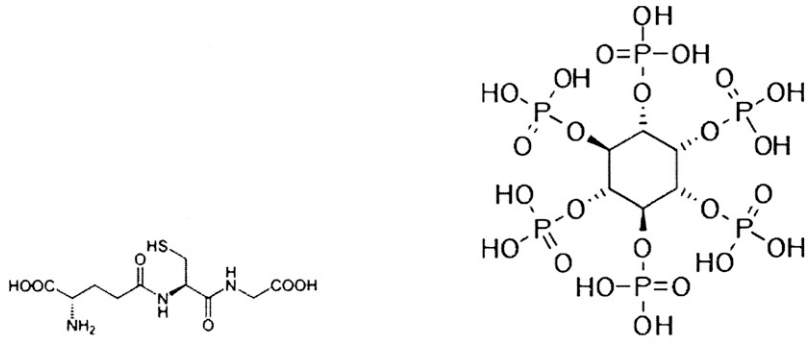


**Figure 4.** Structures of (a) glutathione and (b) phytic acid.

Most of the natural extracts contain flavanoids that provide antioxidant effects and are thus used as skin-lightening agents (69).

*(iv) Vitamins as skin-lightening agents.* Vitamins have been known to improve skin tone and texture, and they have found remarkable acceptance among consumers. Most of the leading brands of skin-lightening agents that are available commercially utilize vitamins or their derivatives as ingredients.

VITAMIN A. Vitamin A has been used for some decades for the removal of spots in Kligman's treatment (70). It is used along with hydroquinone and topical steroids for the treatment of melasma. Tretinoin acts as a skin-lightening agent by inducing exfoliation. Further, it accelerates the loss of epidermal melanin by increasing the turnover rate and by promoting the proliferation of keratinocytes (71,72). However, users of tretinoin suffer from side effects such as burning and increased photosensitization. Retinyl palmitate, a derivative of retinoic acid, is used in skin-lightening cosmetic preparations.

VITAMIN B. Among the classes of vitamins that comprise vitamin B, two have been identified to have skin-lightening activity:

(a) Vitamin B3 (niacinamide): This is one of the most used hypopigmenting agents. It is a well known antioxidant and interferes in melanasome transfer leading to skin lightening. Using co-cultures of human melanocytes and keratinocytes, investigators have shown that niacinamide inhibits the transfer of melanosomes from melanocytes to keratinocytes (73). The results of clinical studies using topically applied niacinamide have demonstrated a reversible reduction in hyperpigmented lesions and increased skin lightness compared with the vehicle alone after four weeks of use (74).

(b) Vitamin B5 (panthenoic acid): A derivative of vitamin B5, calcium pantetheine sulfonate has been observed to interfere with the glycosylation of tyrosinase, thereby leading to depigmenting effects (75).

VITAMIN C. Vitamin C is required for the production of collagen and is a photoprotectant as it deactivates UV-induced free radicals and decreases erythema. Further, Vitamin C also acts as a tyrosinase inhibitor, thereby lightening the skin (76). Although most effective, ascorbic acid is a highly unstable compound. Stable derivatives of ascorbic acid in the

form of sodium ascorbyl phosphate (SAP), magnesium ascorbyl phosphate (MAP), and ascorbyl palmitate are widely used in cosmetic products (77).

VITAMIN E. Vitamin E is the most important lipid-soluble antioxidant in the body. It is abundant in the sebum and acts to absorb the oxidative stress of sunlight and skin exposure. It has been demonstrated that vitamin E provides protection against UV-induced inflammation and hyperpigmentation (78). Vitamin E has also been studied in combination therapies with other vitamins as well as in other classes of skin-lightening compounds (79,80).

Vitamins B, C, and E are used individually or in combination in many skin-lightening treatment therapies.

*(v) Peptides in skin lightening.* Peptides are reported to reduce pigmentation through interaction with the protease-activated receptor 2 (PAR-2) of keratinocytes. PAR-2 activation in involved in cell growth, differentiation, and inflammatory processes and was shown to affect melanin and melanosome ingestion by human keratinocytes (81). The protease-activated receptor-2 upregulates keratinocyte phagocytosis. The peptide-based antagonist for PAR-2 can be used to regulate melanin ingestion by keratinocytes, thus effecting skin-lightening.

Short peptides have also been reported in reducing the enzymatic activity of tyrosinase (82). The use of sericin, a high-molecular-weight soluble glycoprotein from silk, as a tyrosinase inhibitor has also been documented (83). Peptide residues that act as MSH inhibitors have been known to lighten the skin. Soy trypsin inhibitors have been identified as interfering in melanosomal transfer, thereby reducing skin pigmentation (84).

*(vi) Alpha and beta hydroxyl acids and derivatives.* Alpha and beta hydroxyl acids have been the most important class of compounds that are most widely used in cosmetic preparations. These act as superficial chemical peels that target the stratum corneum to improve skin color and tone. They are comparatively pure and inexpensive, and they may be used in higher amounts without many side effects (85). They are generally used in conjunction with other skin-lightening agents to improve performance. Also referred to as fruit acids, they improve skin texture by promoting desquamation or the shedding of the outer layers of the stratum corneum. Alpha hydroxyl acids (AHA) have also been noted to increase the enzymatic activity leading to epidermolysis. They are also employed in microdermabrasion techniques. In addition, they act as moisturizers and promote the synthesis of elastin fibers, leading to improved skin tone. However, care should be taken to neutralize the skin after AHA treatment, as it might cause burning and erythema. The most commonly used AHAs are glycolic, lactic, citric, malic, pyurvic, and salicylic acids and their derivatives.

## THE EFFICACY OF SKIN-LIGHTENING FORMULATIONS

Formulations for skin lightening have been majorly based on o/w emulsions that have a higher aesthetic appeal. The fact that many of the ingredients get better dispersions is also an added feature for the choice of such emulsions. Recently gel-based formulations are being considered for suitability in certain skin types. Efficacy studies for skin-lightening formulations are carried out through clinical trails. Some of the techniques used involve the use of the mexameter, chromameter, spectrophotometer, and VISIA, along with

dermatologist assessment. Also, other skin parameters such as moisturization, texture, barrier integrity, pH, etc, are being evaluated to give picture of skin health after the use of skin-lightening agents. This leads to screening the potentially harmful side effects of hydroquinone-like substances in addition to the high-value claim proposition for the cosmetics industry. With advances in technology in measurement techniques, it is becoming easier to identify the efficacy of formulations in different skin types.

## CONCLUSION

Research in the area of skin-lightening agents in an expanding field, with new ingredients being added to the repertoire with every new discovery. Although tyrosinase inhibition is still the most sought after mechanism skin lightening, newer pathways are being identified. It has been noted that ingredients that interfere with the pathways affecting melanin synthesis and transfer show promise as depigmenting agents. Persistent research into skin lightening has also led to new mechanisms being discovered in recent years.

The aspiration for light skin is on an upward curve and can be satisfied only when the cosmetic in the bottle fulfils the promise of fair skin. A careful and complete investigation of the ingredient on the basis of its efficacy and tolerance to individuals through clinical trails is essential to ascertain that the product delivers the promise.

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